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Pharmacological study and clinical application of new long lasting local anesthetic agents

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THE PHARMACOLOGICAL STUDY AND CLINICAL APPLICATION OF NEW LONG LASTING LOCAL ANESTHETIC AGENTS

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Introduction

Many local anesthetics have been synthesized and introduced into clinical practice since Einhorn's (1) discovery of procaine in 1905. The problem of prolonging the duration of local anesthetics has been investigated by many different approaches.

Two different methods have been used in attempts to increase duration of anesthetic action. One method is by synthesis of different compounds. Most of these agents are more potent and more toxic than procaine hydrochloride and their therapeutic index on intravenous administration is usually lower than that of procaine (2). Recent work which has been done on 2-chloroprocaine (3), procaine ascorbate (4), and meta-hydroxy-procaine (5), shows them as comparing favorably with procaine hydrochloride as to toxicity and potency. Their duration is at least six to seven times that of procaine hydrochloride. This is still not of long enough duration to be of much value in post surgical use, without repeated injection.

The second method of increasing duration of local anesthesia has been by inhibiting absorption of the anesthetic (6). The discovery of the synergistic action of epinephrine with procaine by Braun (7) was one of the earliest methods intended to prolong the anesthetic effect through delayed absorption. This combination is

still used. The duration of the anesthesia is prolonged two to three times.

The use of oil as an immiscible solvent which would slowly release the active ingredients and give prolonged local anesthetic effect was suggested by Yeomans and coworkers (8) in 1928. Different anesthetic agents have been used with an oil solvent combined with from five to ten per cent benzyl alcohol (9,10,11). The first studies of the use of these agents reported a prolongation of anesthetic effect (11,12,13,14) contradictory reports of the prolonged effect of these anesthetics in oil have also appeared in the literature (15,16,17,18,19). Duncan and coworkers (20) and Kelly (21) demonstrated that any prolonged anesthetic effect observed was due to neuro-degeneration caused by the benzyl alcohol. The period of anesthetic action was limited to the period of regeneration of the nerve fibers instead of being due to the pharmacologic activity of the preparation. With solutions of less than 10 per cent benzyl alcohol, there was no neuro-destructive action as shown by failure of any prolonged effect. Kelly's (21) work clinically proved the failure of the anesthetic oil solutions. Other untoward reactions noted with these oil solutions were the formation of abscesses, inflammatory reaction of the tissues, suppuration and necrosis (22, 23).

Other types of solvents used to prolong diffusion include gelatin and polyvenyl pyrolodine (24). With these there was considerable pain on injection and slower healing of wounds in the infil-

trated areas (24,25).

In 1931, Judovick prepared an aqueous solution derived from the pitcher plant, Sarracenia purpurea, and made the observation it was of value in relieving pain of neuralgic origin (26). Toxicity tests showed it to be harmless. Judovich and coworkers showed that the active principle in the distillate from the pitcher plant contained ammonium ion which had a selective blocking effect upon the C fiber potentials of the saphenous nerve of the cat. There was minimal effect on the other fibers of the nerve (26). They report the clinical use of ammonium sulfate to be of value as a local analgesic. Davis and Wilson, in a recent report on the effectiveness of an ammonium sulfate preparation, Dolamin, for the relief of post-operative pain, state that the principle is good but that a more effective analgesic or anesthetic drug is desirable (27).

In 1950. Monash (28) reported a greatly increased duration of local anesthesia using the suspended free base of procaine as compared to procaine hydrochloride. In his preliminary report no toxicity studies were reported. He checked duration of anesthesia by subcutaneous injection into the volar aspect of the arm. The duration of anesthesia with his extemporaneous compounds ranged up to twenty days.

A slight modification of the criteria of the ideal anesthetic (29) may be applied for prolonged anesthetics. These are:

1. "Low toxicity in relatively large doses and absence of idiosyncrosy".

2. "Rapidity of action in order that the injection itself may be painless and that complete anesthesization of the area may be induced within a reasonable length of time". (29).

3. Duration of anesthesia should last until patient has passed the period where complications due to post-operative pain may occur.

4. "There should be no impairment of tissue vitality or retardation of healing".

The purpose of this report is to present toxicity studies on some stable procaine base preparations*. Comparison is made with Efocaine** and with procaine hydrochloride as a control.

Sufficient laboratory and clinical evidence indicating the efficiency and desirability of procaine base preparations and Efocaine as long lasting local anesthetics will also be presented.

Toxicity

Introduction-

The toxicity of any therapeutic agent should be accurately

* Produced by Harvey Laboratories, 5109 Germantown Ave., Phila.Pa.

** Efocaine is the trade mark of E.Fougera Co. Inc., New York City and consists of procaine base 1 per cent, procaine HCl 0.25 per cent, butyl p-amino benzoate 5 per cent, polyethylene glycol-300 2 per cent, propylene glycol 78 per cent, sodium metabisulfite 0.1 per cent, phenylmercuric borate 1:25,000 and water 20 per cent.

determined before it is used clinically. To determine the toxicity, fairly large groups of test animals are necessary. Albino mice, rats, rabbits and dogs were used as test animals in this work. The mouse toxicity tests as developed by Sievers (29) and McIntyre (30) were followed in these experiments. The following rules were observed for the subcutaneous mouse toxicity test (29,30).

(a) Weight of the mouse was 16 to 24 grams.

(b) The period of starvation prior to test was 6 to 10 hours.

(c) The volume of solution was about 0.6 cc., depending on toxicity.

(d) Total volume injected in 6 to 10 seconds.

(e) Injection made under the skin in the dorsal surface of the lumbar region.

(f) Room temperature approximately 70-75 degrees F.

The animals were placed in an air conditioned room to avoid effects of high temperature in reducing the tolerance to the test drug (29). The solutions were injected subcutaneously in the loose tissue of the back.

The $M.L.D_{50}$ is defined as the number of mgs. of compound per kilogram that, when injected subcutaneously, will kill half the test group. The approximate range of the M.L.D. was determined by using small groups of animals, usually 4 - 5 mice. The actual $M.L.D_{50}$ was determined by using test groups of 30 mice until a dosage was found that would consistently kill fifty per cent of the animals. In most cases the mice were alive or dead in a few hours

but the period of observation was lengthened to 5 days time due to the type of long lasting drug used.

Results of mouse toxicity test.

The figures given in Table 1 were obtained with the anesthetics listed. The toxicity ratios were determined according to the following formula (29,30).

$$\text{Ratio} = \frac{\text{M.L.D. of drug}}{\text{M.L.D. of procaine HCl.}}$$

The toxic symptoms usually occurred within 10 minutes after the injection. First symptoms seen were increased respiratory rate followed by great motor excitement and loss of equilibrium. Convulsions usually occurred. Animals surviving the convulsions usually recovered.

The mouse toxicity for Efocaine cannot be entirely determined on the basis of the 1 per cent procaine base and 0.25 per cent procaine hydrochloride present, since according to the formula, 5 per cent butyl p-aminobenzoate is also present.

The toxicity of butyl p-aminobenzoate has been found to be quite high when compared to procaine hydrochloride (31). The amount of procaine base and procaine hydrochloride contained in Efocaine is far below the $M.L.D._{50}$ found in toxicity studies for these two compounds.

Animals which survived the convulsions or early respiratory depression for periods of 20 to 30 minutes usually recovered, however, a few injected with Efocaine died 24 to 30 hours later.

Table I.

L.D.$_{50}$ Determination on White Mice

Drug	Procaine content per cc.	Number of animals	M.L.D. gm/Kgm.$_{50}$	Approximate toxicity ratio $\frac{\text{M.L.D. of drug}}{\text{M.L.D. of procaine HCl}}$
4-Amino-benzoyl-diethylamino-ethanol HCl (procaine HCl)	20 mg/cc (2%)	30	0.7 ± 0.3	1.0000
Procaine base	100 mg/cc	30	3.0 ± 0.4	4.0000
Procaine HCl 2% Procaine base 2%	20 mg/cc procaine HCl 20 mg/cc procaine base	30	2.0 ± 0.2	3.0000
Duricaine (2% procaine base)	20 mg/cc	30	3.0 ± 0.4	4.0000
Efocaine	2.5 mg/cc procaine HCl 10.0 mg/cc procaine base (also has 50 mg/cc butyl p-aminobenzoate)	30	.11 procaine .044 butyl p-aminobenzoate	0.0015

Intravenous Toxicity

It is generally agreed by numerous investigators that procaine hydrochloride is one of the safest and most useful agents for local infiltration or nerve blocking. According to Schumacker (32), the intravenous lethal dose of procaine hydrochloride is only one tenth as great as the subcutaneous lethal dose. The intramuscular median lethal dose is smaller than the subcutaneous dose while the intraperitoneal dose is almost twice as large (32).

In this experimental work the toxicity of procaine base suspensions and Efocaine are compared with that of procaine hydrochloride and saline by intravenous administration into mongrel dogs. The dogs were given Sodium Pentothal as a general anesthetic. Mean arterial blood pressure was measured by a kymographic recording mercury manometer which was connected to a cannula in the common carotid artery. Six per cent citrate solution was used to prevent clotting. Respiration was recorded by means of a trachea cannula connected by rubber tubing to a bromoform manometer. This allowed comparison of the hemodynamic and respiratory effects of the different anesthetic solutions when injected into the cannulated femoral vein of the dog. All intravenous injections were made as rapidly as possible through a 25 gauge needle. Ten different dogs were used for this study.

Results-

Procaine hydrochloride in increasing doses of 50 mgms. each was

injected intravenously. There was some variation in the lethal dose in different dogs. Figure 1 shows the effect of 50 mgm. of procaine hydrochloride. There was very little effect on either blood pressure or respiration. When the amount injected was increased to 100 mg. there was a little drop in blood pressure and no visible effect on respiration. As shown in Figure 2, the drop in blood pressure occurred within 5 to 15 seconds after the injection was started. The return of the blood pressure to the former level or a new level was reached within 2 to 3 minutes. With small or large amounts of procaine hydrochloride the blood pressure drop occurred without any demonstrable change in rate. No irregularities were noticed. With an increased dose of procaine hydrochloride up to 150 mg (Figure 3) there was more of a drop in blood pressure and some slowing of respiratory rate with a decrease in amplitude of respiration. In most dogs the lethal dosage ranged from 20 to 30 mgm. of procaine hydrochloride per kilogram. Figure 4 shows the blood pressure drop following 200 mgm. of procaine hydrochloride in an eight kilogram dog. Respiration showed an immediate increase in rate and amplitude followed by respiratory arrest prior to cardiac arrest.

A combination of 2 per cent procaine hydrochloride plus 2 per cent procaine base was relatively non-toxic when compared to procaine hydrochloride alone. Figure 5 shows the effects of 8 ml. of this solution. There was a slight drop in blood pressure as shown by the recording, while no visible respiratory effect occurred.

Five ml. of Duracaine which contains 2 per cent procaine base, proved to have very little effect on both respiration and blood pressure as illustrated in Figure 6.

The toxicity of procaine base suspensions is very much less than that of procaine hydrochloride and Efocaine as will be shown later. Forty mgm. per kilograms, as shown in Figure 7, had no visible effect on blood pressure and very little, if any, on respiration. On increasing the dose to 120 mgm. per kilogram as shown in Figure 8 only slight drops in blood pressure were seen. There is a slight decrease in amplitude of respiration.

Amounts up to 150 mgm per kilogram had very little effect as shown by Figure 9. There was a slight fluctuation in systolic and diastolic pressures, with a slight increase in mean blood pressure. No visible effect on respiration was seen.

The effects of increasing amounts of Efocaine intravenously are shown in Figures 10,11,12 and 13. With increasing dosage there was usually a slight increase in amplitudes of respiration which was then followed by a decrease in amplitude and rate. Blood pressure was depressed.

Four ml. (Figure 12) had a marked effect on both respiration and blood pressure, while 5 ml.(Figure 13) caused respiratory arrest and drop in blood pressure followed by cardiac arrest and death of the dog. On the basis of anesthetics contained in Efocaine this toxic dose, which is fairly representative of that found in most dogs, was found to be 21 mgm. per kilogram of butyl p-aminobenzoate plus 5 mgm.

per kilograms of procaine base and 1.5 mgm. per kilogram of procaine hydorchloride. On the basis of these previous experiments on procaine base and procaine hydrochloride, the toxicity of Efocaine must be due to the 5 per cent butyl p-aminobenzoate present and which, according to Beutner (31), is about 20 times more toxic than procaine hydrochloride.

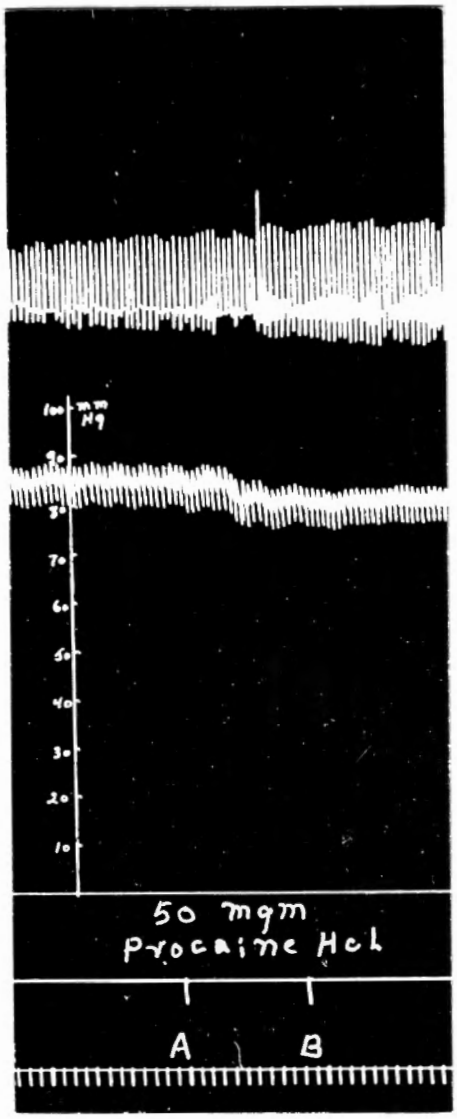

Figure 1.

Kymographic recording of intravenous effect of 50 mgm. of procaine hydrochloride on respiration above and mean blood pressure below. Injection started at A and finished at B. Time interval is 5 seconds recorded on bottom line. Weight of dog 8 Kgm.

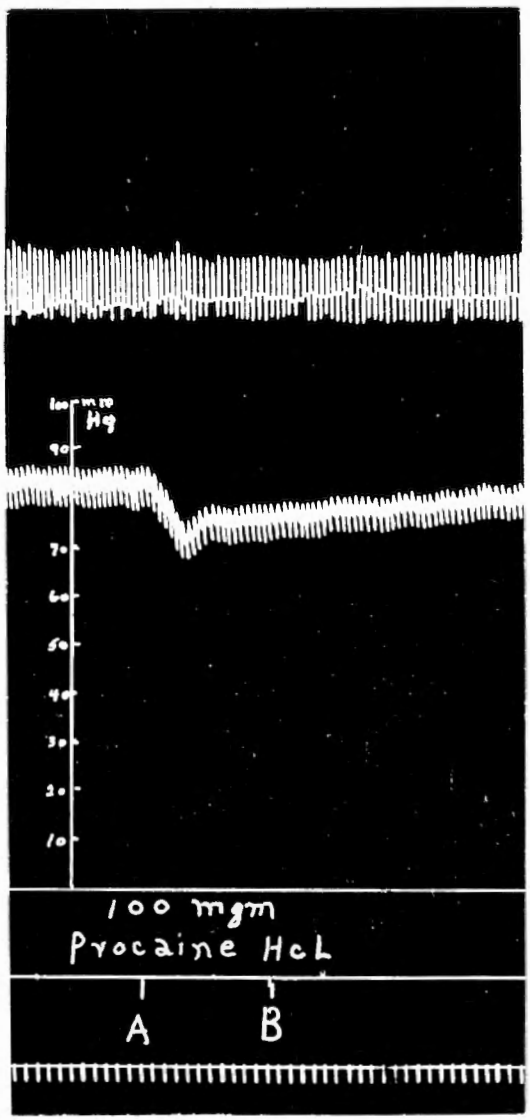

Figure 2.

Kymographic recording of effect of 100 mgm. of procaine hydrochloride given intravenously. Injection started at A and finished at B. Respiration was recorded above and blood pressure below. Time interval 5 seconds. Weight of dog 8½ Kgm.

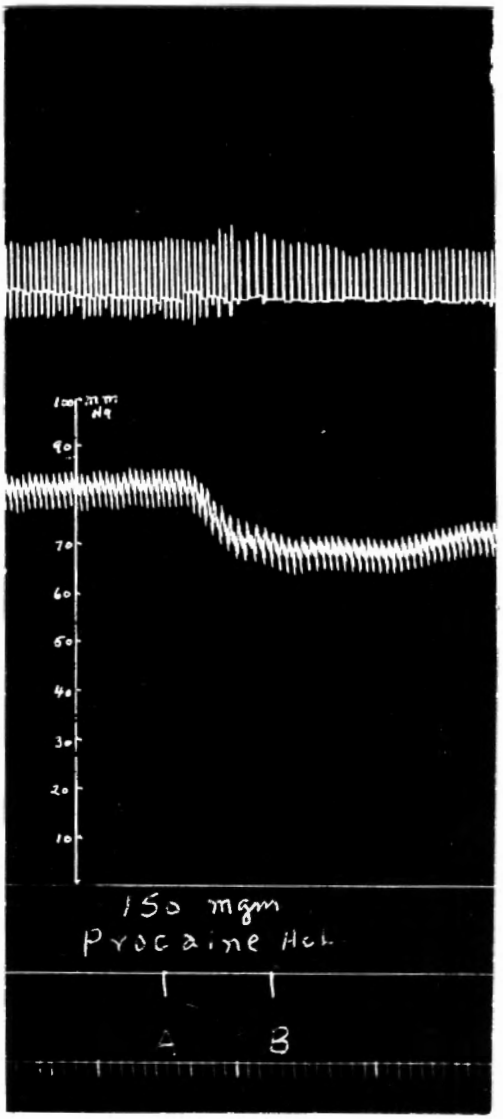

Figure 3.

Kymographic recording of effect of injecting 150 mgm. procaine hydrochloride intravenously, starting at A and finishing at B. Respiration was recorded at top, with the blood pressure just below the respiration. Time interval 5 seconds. Weight of dog 7 Kgm.

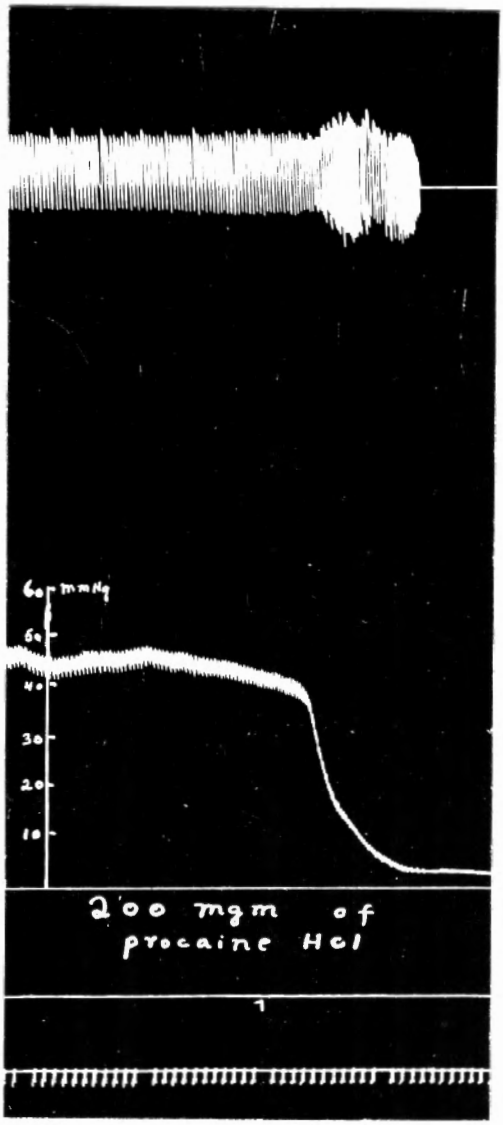

Figure 4.

Recording of effect of 200 mgm. procaine hydrochloride injected intravenously in an 8 Kgm. dog. The mark on the second line from the bottom shows point of beginning of injection. Respiration recorded at top and blood pressure below. Time interval 5 seconds on bottom line.

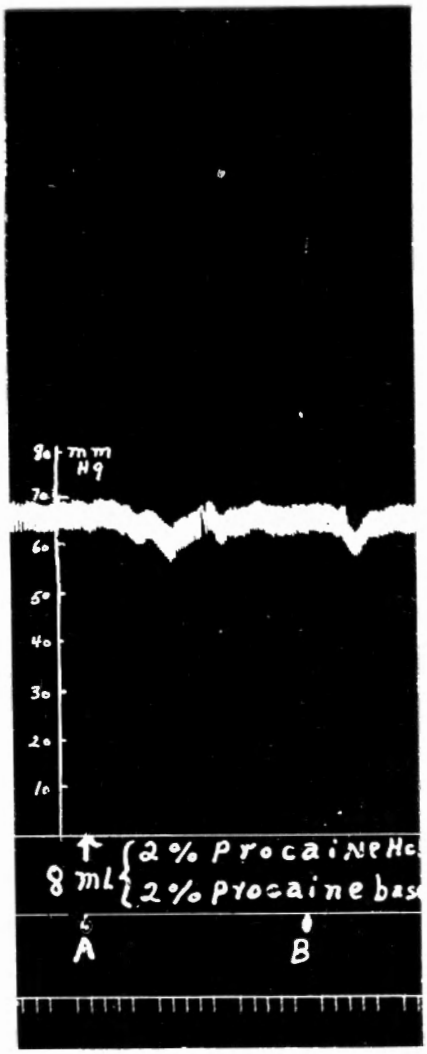

Figure 5.

Intravenous injection of 160 mgm. procaine hydrochloride plus 160 mgm. procaine base was started at A and finished at B. Recording shows effect on mean blood pressure. Time interval 10 seconds. Weight of dog 7 Kgm.

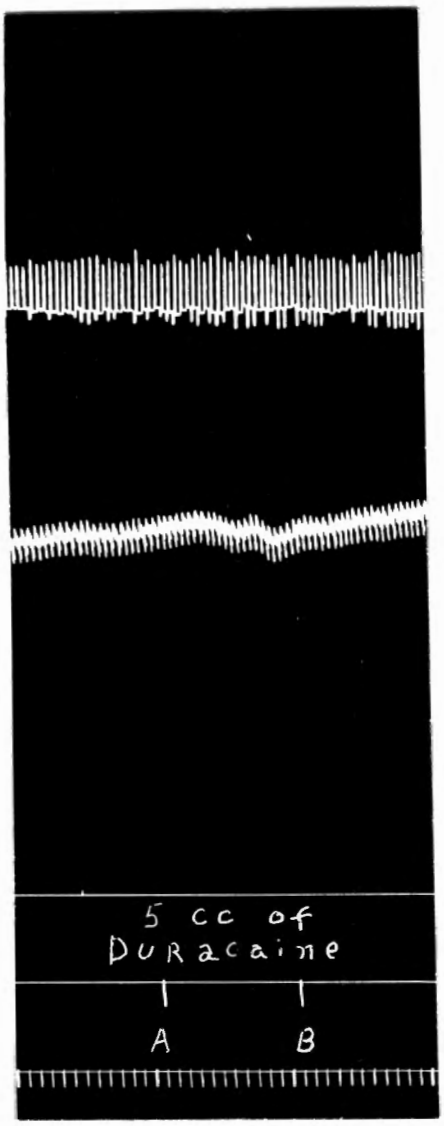

Figure 6.

Effects of Duracaine on respiration and mean blood pressure. Intravenous injection started at A and finished at B. Time interval 5 seconds. Weight of dog 7 Kgm.

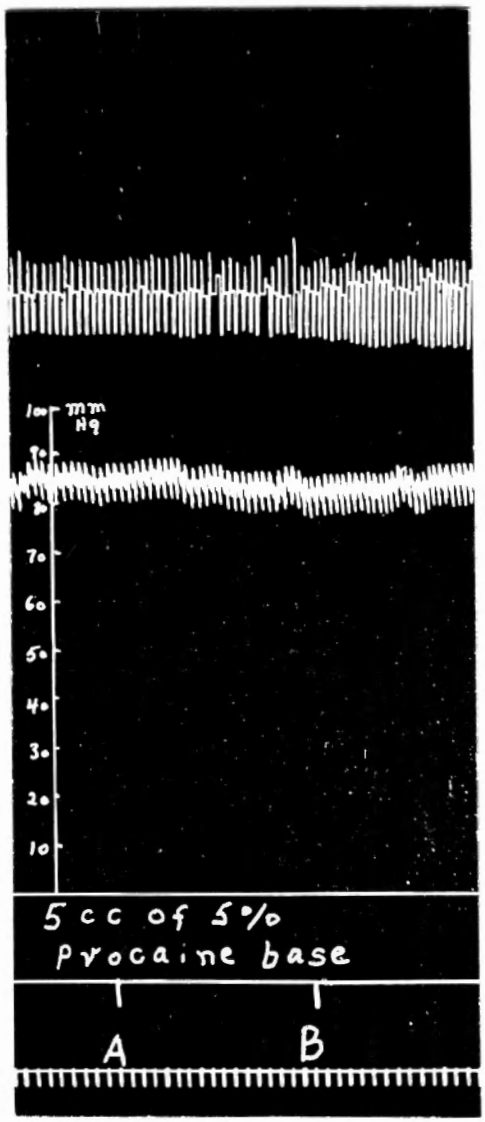

Figure 7.

Effects of 250 mgm. procaine base suspension injected intravenously between A and B. Respiratory rate as recorded at the top shows a slight increase in rate. Mean blood pressure of 80 to 90 mm. Hg. shows little change. Weight of dog 6.25 Kgm. Time interval 5 sec.

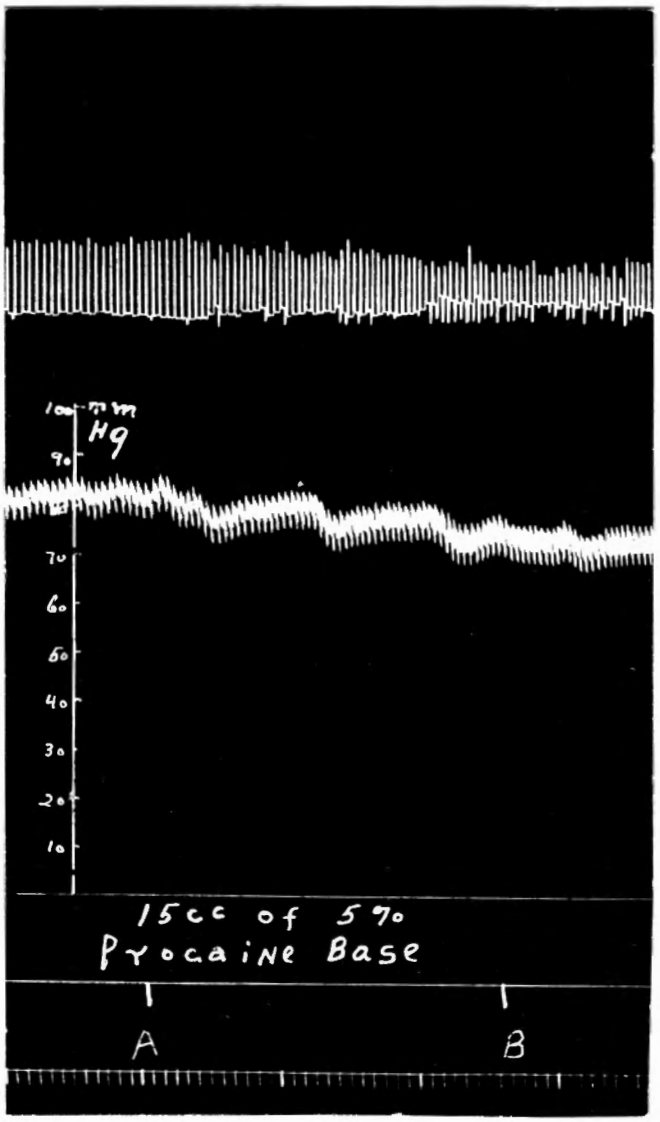

Figure 8.

A total of 750 mgm. of procaine base in 5 per cent solution was injected intravenously in a 6.25 Kgm. dog. Injection was started at A and completed at B. Mean blood pressure was recorded below respiration was recorded at the top of the record. Time interval 5 seconds.

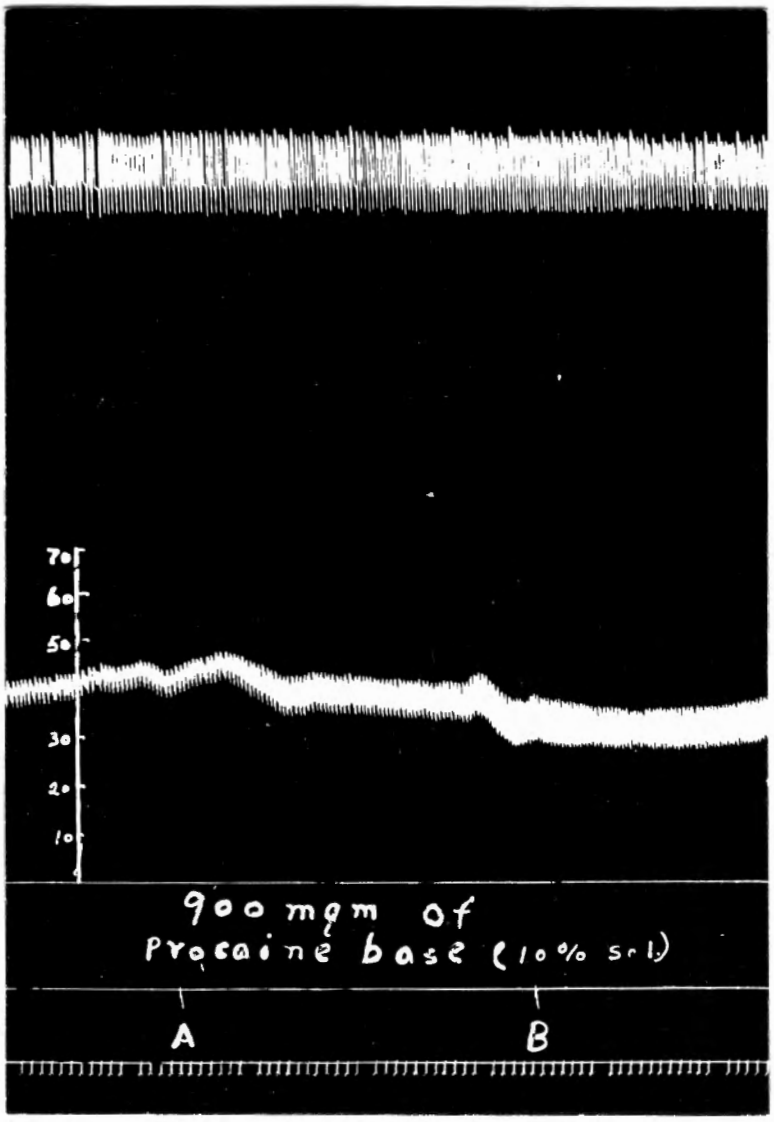

Figure 9.

Intravenous injection of a total of 900 mgm. of procaine base suspension started at A and completed at B. Respiration recorded at top shows little effect. Mean blood pressure recorded below respiration shows a slight increase. Weight of dog 6 Kgm. Time interval 5 seconds.

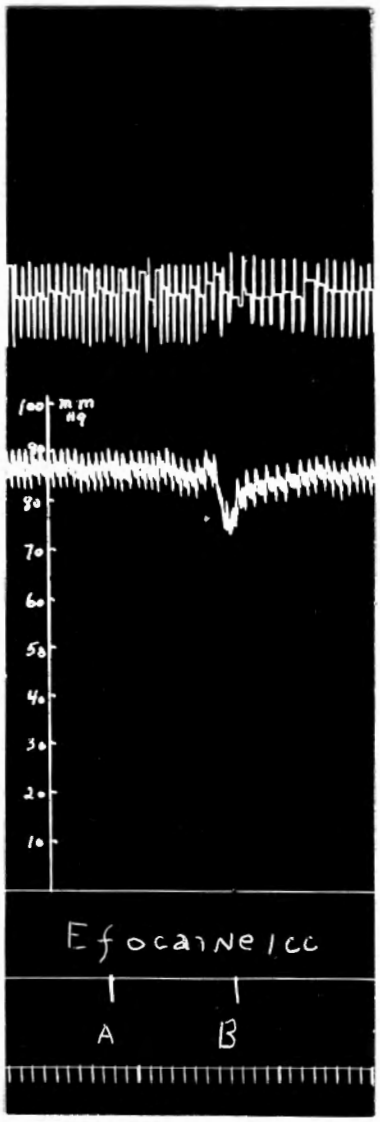

Figure 10.

One ml. of Efocaine injected intravenously from A to B. Respiration was recorded in upper part of tracing and blood pressure was recorded below respiration. Weight of dog 9 Kgm. Time interval 5 seconds.

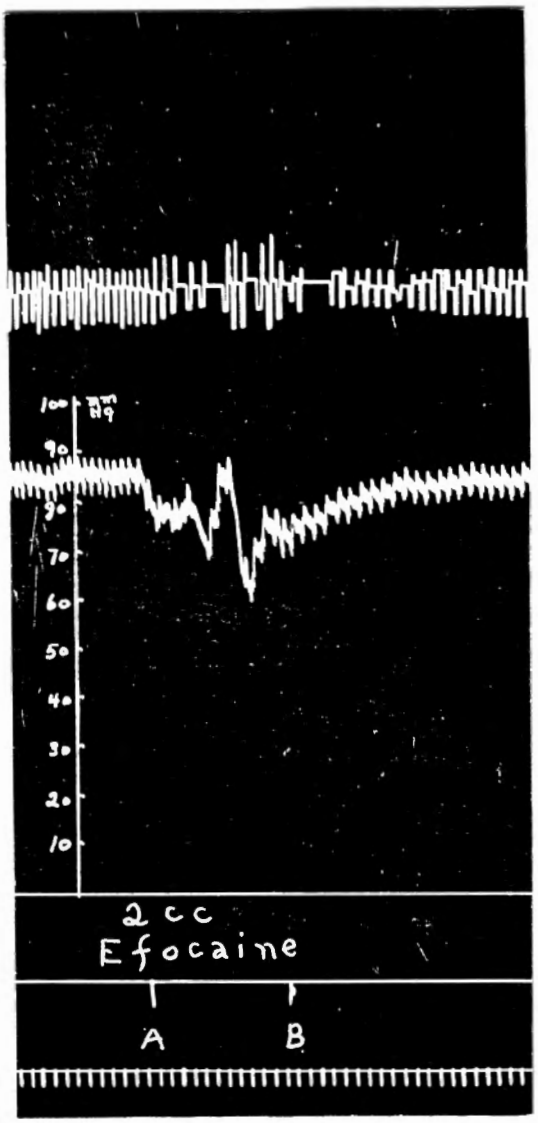

Figure 11.

Two ml. of Efocaine were injected intravenously at A to B. Respiration at the top of the record shows decreased amplitude with some short periods of apnea. Blood pressure was decreased but returned to normal. Weight of dog 9 Kgm. Time interval 5 seconds.

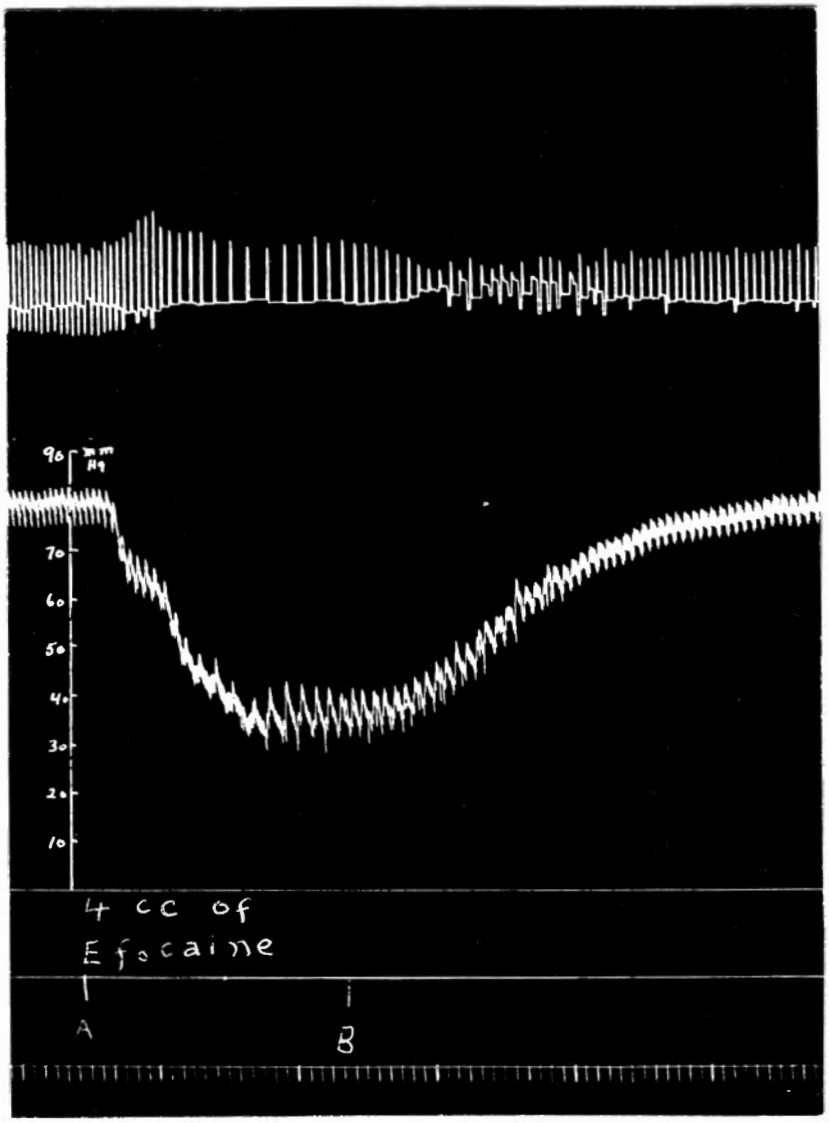

Figure 12.

Injection of 4 ml. of Efocaine intravenously from A to B. A sharp drop in blood pressure occurred. Respiration in upper part of tracing shows at first an initial increase in amplitude followed by a decrease in amplitude and rate. Weight of dog 10 Kgm. Time interval 5 seconds.

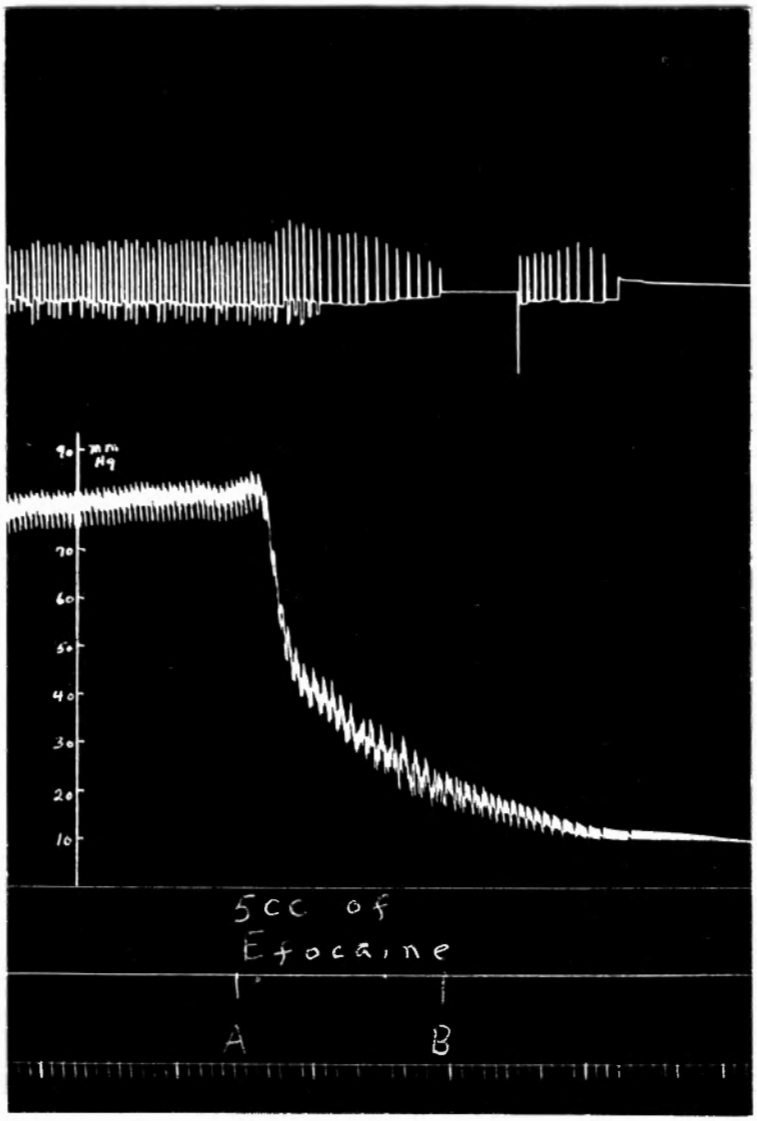

Figure 13.

Respiratory failure and cardiac arrest following injection of 5 ml. of Efocaine intravenously from A to B. Weight of dog 11.9 Kgm. Time interval 5 seconds.

Comparison of intravenous toxicity of procaine hydrochloride, procaine base and Efocaine was also made by injecting the various anesthetics into the ear veins of 2 Kg. rabbits. No general anesthetic was used. Constant intravenous injections, given so as to cause respiratory paralysis or convulsions in 6 to 7 minutes were used. This gave the most consistent results in absorption (33).

The intravenous Efocaine was toxic to the extent that one to one and one half ml. were lethal when injected into the ear veins of the rabbits. There appeared to be respiratory paralysis, collapse and death before convulsions had time to develop. This high toxicity as compared to procaine base is apparently due to the 5 per cent butyl p-aminobenzoate present in Efocaine.

The convulsive dose of procaine hydrochloride was in the range of 60 mg. per kilogram of body weight in the rabbits. Procaine base suspension was relatively non toxic in that 410 mg. per kilograms were necessary to produce convulsions.

Results are shown in Table 2. These were obtained from groups of three rabbits for each anesthetic.

Table II.

Comparative Respiratory and Cardiovascular
Toxicity of Procaine HCl. Procaine Base and Efocaine on Rabbits

Drug	Total mg/Kg. injected	Recovery
Procaine HCl	60 mg. ± 05.0	100%
Procaine base	410 mg. ± 80.0	100%
Efocaine	12.5 mg. procaine 50.0 mg. butyl p-aminobenzoate	0%

Anesthetic Potency Measured on Sciatic Nerve of Frog.

Conduction anesthesia involves the penetration of a nerve sheath followed by paralysis of a nerve trunk by an anesthetic. The obvious way of securing this condition on an experimental basis, is to expose the nerve of an animal and immerse it in a solution of the anesthetic (34). The muscle-nerve preparation of the frog, consisting of the gastrocnemius muscle with the lower third of the femur attached together with the entire sciatic nerve from spinal cord to knee, has some merit. Similar techniques have been described by McIntyre and his associates (35,36). Immersion of the nerve in anesthetic solution followed by stimulation by means of a faradic current results in a motor reflex if the anesthetic is ineffective.

The contraction of the muscle produced by the motor reflex may be recorded on a kymograph by means of a writing lever attached to the tendon of the muscle.

Experimental observations.

Preparations were prepared so that the gastrocnemius muscle was immersed in a frog Ringer preparation. The sciatic nerve was suspended in the anesthetic solution in a separate chamber for 1 to 2 minutes. The standard stimulation was applied.

Procaine hydrochloride caused prompt interruption of conduction, the minimun effective dose being about 0.75 per cent concentration. Efocaine likewise was prompt in action, acting in a minimun effective

dose of 0.1 per cent of the butyl p-aminobenzoate present. Procaine base had very little if any effect, on the opposite sciatic nerve of the same animal.

This lack of effect is similar to that found for procaine amide (36) which when tested by intracutaneous and subcutaneous injections in man, had a local anesthetic action.

Anesthetic Potency Measured by Eye Lid Reflex Method

Anesthesia of the rabbit's eye lid has been used as a method of testing anesthetic activity of injected anesthetics. This method also affords an excellent opportunity for studying the tissue reaction grossly by observing the conjunctival reactions.

Technique

The rabbit was placed in a stall or box to prevent excessive movement, The conjunctiva of both eyes were carefully examined in order to be able to check for any irritation or pathological effect.

A 25 gauge needle was used and the anesthetic was injected into both upper and lower lids until the conjunctival sac buldged on the inside of the lid. It was found one half ml. of the solution being tested, injected into each lid was the optinum amount.

Anesthesia was observed by gently touching the cilia of each eye lid with a small camel hair brush. Care was taken to exclude visual reflexes by approaching the eye lash from above. Criteria for local

anesthesia was absence of wink reflex on stimulation of the cilia of eye lid.

One eye of each rabbit was used as a control. The wink reflex was checked after injection of the solutions and then every 30 minutes for the duration of anesthesia. The conjunctiva was also inspected for hyperemia and tissue reaction.

The results of the anesthetic potencies of the compounds tested are shown in Table III. The end point or disappearance of anesthesia varies with this method of testing, due to animal variation and tissue reaction with some of the anesthetics. With 5 per cent and 10 per cent procaine base, and with Efocaine, there was hyperemia and edema of the conjunctiva 24 hours after injection. This cleared in all cases in 2 to 3 days. No tissue slough was seen up to 3 weeks time.

Table III

Anesthetic Potency Measured by Eye Lid Reflex of Rabbits

Drug	Solution	Number tests	Approximate duration of anesthesia	Conjunctival Reaction	Gross tissues Reaction of membranes after one day
Procaine HCl	2%	5	35 minutes	+	0
Procaine base	1%	5	6 hours	+ +	0
Procaine base	2%	5	6½ hours	+ +	0
Procaine base	5%	5	17 hours	+ + +	Slight congestion
Procaine base	10%	5	22 hours	+ + + +	Hyperemia and edema of eyelid
Duricaine		5	7 hours	+ +	Slight congestion
Procaine base + Procaine HCl	2%	5	6 hours	+ +	slight congestion
Efocaine	1% procaine base, 0.25% procaine HCl, 5% butyl p-aminobenzoate	5	32 hours	+ + + +	Edema and hyperemia

Anesthetic Potency in Man by Intradermal Injection

One of the best methods for evaluating the anesthetic potency of an anesthetic is by the technique of Sollman (37) and reported on by McIntyre and coworkers (30), in their toxicity studies. In this experimental work volunteer sophomore medical students and members of the department of Physiology and Pharmacology were used. The rate of onset of anesthesia, duration of anesthesia and tissue reactions were compared following the intracutaneous injections of procaine hydrochloride 1 per cent, procaine base in concentrations of 1, 2,5, and 10 per cent and a combination of 2 per cent procaine hydrochloride plus 2 per cent procaine base. Efocaine was not injected due to warning against such injections in the literature (6).

Injections in 0.25 ml. amounts were injected intracutaneously into the volar aspect of the forearm. From 4 to 8 wheals were made upon each individual. These injections were distributed over as wide an area as possible consistent with equalities in dermal thickness. When testing for block of pain sensation, the test subject's head was turned so that he could not see the experimentor and the different areas were tested for loss of sharp pain sensation with a needle point. Sterile technique was used throughout the experiment.

The results of approximately 124 tests are shown in Table IV. Procaine hydrochloride 1 per cent was used for comparison and as a control. Only slight erythemia and slight initial pain were noted with procaine hydrochloride, and with the procaine base solutions

up to and including the 5 per cent solution. However, with the intracutaneous injection of a 10 per cent solution of procaine base there was a mild to severe burning sensation which disappeared in a few minutes. A blister-like bleb formed in 15 to 20 minutes. This disappeared in a few hours but left an area of pitting and scar tissue which is still present in the author's arm after 1 year's time. The area was anesthetized for a period of four to six days, however. The 10 per cent procaine base was not injected in the students after the above observation was noted.

Isotonic saline in 0.25 ml. amounts was injected to rule out the production of any loss of sensation due to local tension. All of the procaine base solutions were effective considerably longer than was procaine hydrochloride. The 10 per cent procaine base is of a too high a concentration to be used intracutaneously. The large increase in wheal size after intracutaneous injection of 10 per cent procaine base solution would indicate a hypertonic effect. This concentration causes inflammation and necrosis with subsequent scar formation when injected intracutaneously. The 2 and 5 per cent procaine base solutions appear to be worthy of clinical trial.

Table IV.

Anesthetic Potency Determined by Intracutaneous Tests on Man

Drug	% Solution	Duration			Initial Pain	Erythema	Scar Formation
		Min.	Max.	Mean			
Procaine HCl	1%	15 min.	20 min.	17 min.	+ +	+	0
Procaine base	1%	10 hrs.	12 hrs.	11 hrs.	+ +	+	0
Procaine base	2%	15 hrs.	21 hrs.	20 hrs.	+ +	+	0
Procaine base	5%	3 days	4 days	$3\frac{1}{2}$ days	+ +	+ +	0
Procaine base	10%	4 days	6 days	$4\frac{1}{4}$ days	+ + + +	+ + + +	Marked edema plus scar formation
Procaine base Procaine HCl	2% 2%	16 hrs	20 hrs	18 hrs.	+ +	+	0

Comparison of Anesthetic Potency of Procaine Base Solutions and Efocaine by Means of Subcutaneous Injections.

Preliminary reports on the duration of subcutaneous injection of procaine base have been made (28). Ansbro and associates have also reported on the duration of Efocaine (6).

Comparison of the duration and effects of procaine base, procaine hydrochloride and Efocaine was done on volunteer medical students. one ml. of Efocaine was injected subcutaneously in the volar aspect of the forearm and 1 ml. of procaine base or procaine hydrochloride were injected into the corresponding area of the other arm. Results are reported in the nearest whole days in Table V.

With the injection of the Efocaine solution there was usually a short period of burning, lasting 2 to 3 minutes. Anesthesia occurred in a few seconds. With the injection of 10 per cent procaine base solution there was no initial burning on injection but in a few minutes a severe burning occurred which lasted from 15 to 25 minutes. Anesthesia was present within a few seconds.

The subcutaneous injections of the 5 per cent and 2 per cent solutions of procaine base cause very little burning after injection. With the 2 per cent procaine hydrochloride and 2 per cent procaine base, no burning occurred,

Hyperemia occurred after the subcutaneous injection of Efocaine and also after the 10 per cent procaine base, being greater with Efocaine. This was maximal at 24 hours after injection with the above solution. At 48 hours the hypermia in both arms had cleared

and there was no gross evidence of any reaction. Figure 14 is a color photograph of the hyperemia due to Efocaine and 10 per cent procaine base.

Very little reaction was seen following injection with 5 per cent procaine base, 2 per cent procaine base, or with a combination of 2 per cent procaine base plus 2 per cent procaine hydrochloride.

Table V.

Anesthetic Potency Determination by Subcutaneous Tests on Man

(Twelve Injections of Each)

Drug	Concentration per cent	Duration of Anesthesia			Hyperemia
		Minimal	Maximal	Mean	
Procaine HCl	1%	20 min.	40 min	25 min.	0
Procaine HCl Procaine base	2% 2%	1 day	5 days	3 days	+
Procaine base	2%	1 day	6 days	4 days	+
Procaine base	5%	3 days	12 days	8 days	+ +
Procaine base	10%	8 days	16 days	12 days	+ + + +
Efocaine	1% procaine base, 0.25% procaine HCl, 5% butyl p-aminobenzoate	4 days	17 days	14 days	+ + + +

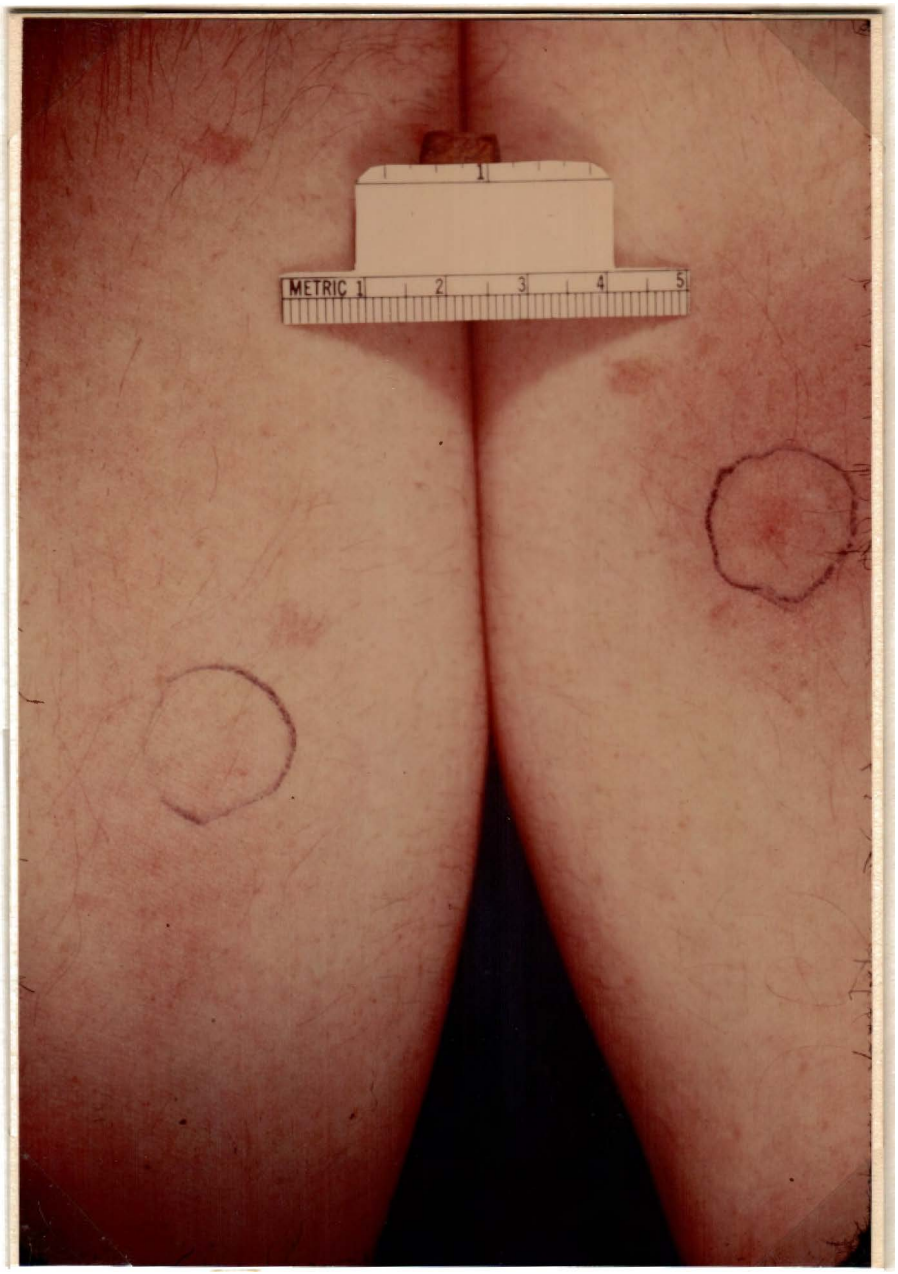

Figure 14.

The hyperemia occurring on the volar aspect of arm 24 hours after subcutaneous injection of 1 ml. of Efocaine on the right and 1 ml of 10 per cent procaine base on the left. More reaction was seen with Efocaine.

Pathologic Effects of Procaine Base Suspensions and Efocaine.

Preliminary studies on the effects of procaine base on tissues have been done by Segal (38). He reports no evidence of pathological changes in the breast, lung, brain, kidney, liver and spleen of animals injected daily for 6 weeks. There were no deaths and the animals continued to gain weight to the same extent as the controls. Histologically there were slight granulomatous infiltrations of the muscle as would be encountered with any innocuous foreign body injection, chronically administered, The doses employed, on a weight for weight basis are 200 to 300 times the recommended therapeutic dose for humans (38).

Weinberg (39) has made a study of the effects of Efocaine upon nerves, muscles, skin and subcutaneous tissues of rabbits, guinea pigs and rats in both acute and chronic experiments. He reports that subcutaneous, intramuscular and perineural injection of Efocaine produces no significant permanent damage to the tissues involved. Injection of Efocaine did not result in a foreign body giant cell reaction and there was no apparent permanent storage of Efocaine at the site of injection.

In this work, comparison of the effects of tissue were made following subcutaneous, intramuscular and perineural injection of procaine base suspensions, procaine hydrochloride, Efocaine and isotonic saline. Six dogs, 18 rats and 12 rabbits were used. In the dogs a total of 1 ml of the anesthetic was injected into each of

the following: the sciatic notch, the muscles of the posterior thigh of the opposite leg and subcutaneous tissues of the abdominal wall. In rats and rabbits 0.5 ml. was used for the above injections. Isotonic saline was used as a control. One half of the rabbits and rats were sacrificed at 24 hours and the others at seven to 14 days following injection. The dogs were sacrificed two to three weeks after injection.

Dr. Morton Kulesh of the Pathology Department of the University of Nebraska College of Medicine, did microscopic studies of all of the tissues.

"In animals autopsied up to 21 days following injection of Efocaine, procaine base, procaine hydrochloride and saline the following was found: with all four agents the nerve fiber bundles showed no histological changes. In the connective tissue covering around the nerves there was minimal infiltration with scattered lymphocytes. The degree of inflammatory reaction was judged as mild".

"Sections of muscle from animals autopsied at 24 hours showed no recognizable inflammatory reaction with either Efocaine, 5 per cent procaine base, 2 per cent procaine hydrochloride or isotonic saline".

"Section of skeletal muscle from dogs autopsied at 21 days after being injected with Efocaine showed the following: in the connective tissue adjacent to one portion of the muscle there were several areas of granulatory type tissue containing primarily lymphocytic and plasma cells as well as numbers of histiocytes. Little

acute inflammatory reaction was seen. No foreign body reaction was seen. In some areas there was extension of this inflammatory reaction into the immediately adjacent muscle bundles. However, muscle bundles at some distance appeared normal. A few areas of chronic inflammatory infiltration were seen in the fibrous septa between muscle bundles. The severity of this inflammation was graded as mild to moderate."

"Similar preparations of skeletal muscle injected 21 days previously with 2 ml. of 10 per cent procaine base showed the following reaction: throughout many areas there were large accumulations of inflammatory cells and in the center of some of these were areas of coagulation type necrosis. The inflammatory reaction was quite intense and was chronic in type although some polymorphonuclear leukocytes were present. Some areas showed no necrosis but simply the collection of inflammatory cells. No identifiable foreign body was seen. Some of the muscle fibers in the region of the more severe inflammatory reaction appeared to be degenerating. Otherwise the muscle fibers did not appear remarkable. The intensity of the reaction is graded as severe".

No inflammatory reaction was seen in muscle tissue 7 days and 21 days after injecting procaine hydrochloride or saline.

Microscopic study of sections of skin and subcutaneous tissues after being injected with procaine base suspensions and Efocaine showed similar reactions except for that of 10 per cent procaine base, the results of which will be given later. Subcutaneous tissue

sections made 24 hours after Efocaine injection showed several large areas of coagulation type necrosis surrounded by inflammatory reaction which was of a granulation tissue type and contained primarily chronic inflammatory cells. The reaction was graded as severe.

Sections of subcutaneous tissue and skin from dogs and rats injected 24 hours previously with 5 per cent procaine base suspensions showed similar reactions as occurred with Efocaine. Deep in the subcutaneous tissues there was a rather large area of coagulation type necrosis. In this area were several areas of inflammatory reaction, both acute and chronic in type. The intensity of the reaction was graded as moderate to severe because of the presence of necrosis.

The reaction in subcutaneous tissue after injection with 10 per cent procaine base was judged as severe, both after 24 hours and 14 days, due to the degree of inflammatory reaction and presence of areas of necrosis. No foreign body reaction was seen. In subcutaneous tissue injected with procaine hydrochloride and saline no inflammatory reactions were seen.

Sections of skin and subcutaneous tissue from animals autopsied 14 days after injection with Efocaine showed an area of granulomatous inflammation in the deeper portion which contained many nuclear fragments and many polymorphonuclear leukocytes. This appears primarily chronic in type. The degree of inflammatory reaction is considered to be mild to moderate. This inflammatory reaction involves the muscle layer.

Discussion of Toxicity and Anesthetic Potency

The toxicity of procaine hydrochloride has been determined by numerous investigators and found to be relatively safe when used as a local anesthetic (32). The toxicity of a local anesthetic agent depends on the concentration reaching the blood stream. This concentration is determined by the rate with which the agent reaches the intravascular fluid and also by the amount of the intravascular fluid. The rate with which the anesthetic is absorbed into the interstitial and intracellular fluid also determines the concentration in the intravascular fluid. The rate of detoxification must also be considered.

Many efficient local anesthetics are ester-like combinations of an amino alcohol with p-aminobenzoic acid or with some other benzoic acid derivative. Procaine contains aminobenzoic acid. Modification in the procaine structure causes important changes in the physiological action of the resulting compounds. Three modifications which change the procaine type molecule and affect duration of activity and potency are: the alkyls on the amine may be changed; the alkylene chain connecting the amine and the benzoate portion may be changed; or substituents may be introduced into the benzene ring. Unfortunately, when the duration of anesthesia of a compound is increased by any of the means listed above, there is usually a relatively greater increase in either the toxicity or the irritation and sometimes in both (34).

Monosubstitution on the p-amino group of the procaine type molecule greatly increases the duration of action as has been shown by a comparison of the actions of procaine and pontocaine which has butyl aminobenzoic acid instead of aminobenzoic acid and which increases the duration of anesthesia considerably. The substitution of a butyl group in this particular location of the molecule appears to raise the anesthetic potency and toxicity considerably. The potency of pontocaine being approximately 150 times that of procaine (31).

The toxicity of butyl p-aminobenzoate is reflected in the results found in this experimental work on Efocaine. Intravenous injections on dogs and rabbits show that the toxicity of Efocaine is greater than that of procaine hydrochloride and much greater than that of procaine base suspensions.

It has long been thought that the liver was the principle site of detoxification of local anesthetics. However, the discovery in plasma of an enzyme that catalyses the hydrolysis of procaine to diethyl aminoethanol and p-aminobenzoic acid, changed the thinking along these lines (34).

Rovenstein and co-workers (41) showed that when procaine hydrochloride solution was injected intravenously, it was very rapidly broken up into diethyl aminoethanol and p-aminobenzoic acid. The latter appeared in the urine largely unaltered and could easily be tested for with Bratton Marshall reagent.

Kalow (42) has shown that one liter of human serum can hydro-

lyze, under optimal conditions in vivo, about 6.7 mgm. of procaine hydrochloride per minute while pontocaine was hydrolyzed 4 to 5 times more slowly than procaine.

These findings may account for part of the increased toxicity of Efocaine over that of procaine hydrochloride and procaine base.

The fact that procaine base may be slowly released from a depot when injected subcutaneously has been proved by Monash (43). He injected .5 gm. of procaine base in 1 ml. of water subcutaneously. Immediate anesthesia resulted and lasted for 14 days. He showed that the anesthesia was due to continuous presence of procaine by testing urine for p-aminobenzoic acid by means of the Bratton Marshall reagents. He found p-aminobenzoic acid present as long as anesthesia lasted showing that a slowly absorbable depot of procaine was formed by the injection.

This slow release of procaine base partially accounts for the high $M.L.D._{50}$ which was found for it. (See Table I).

The fact that the frog sciatic nerve is immediately blocked by procaine hydrochloride has been shown by many investigators (44.45). These results were verified in this work. Efocaine was also found to be immediately effective whereas procaine base was practically nil in activity on the frog sciatic. This lack of activity has also been noticed with procaine amide (36) but which was found to have anesthetic activity when injected subcutaneously.

In comparison by means of eyelid reflex method Efocaine was found to have longer duration than either procaine hydrochloride or

procaine base. Hyperemia of the conjunctiva occurred with Efocaine and 5 per cent to 10 per cent procaine base solutions. (See Table III). This method is a very convenient way of checking gross tissue reactions by observing any conjunctival reaction. The hyperemia was not evident with any of the preparations after 2 to 3 days.

Results of intracutaneous tests with procaine hydrochloride and procaine base as shown in Table IV, indicate the prolonged effect of procaine base suspensions. It should be noticed that when 10 per cent procaine base was injected intracutaneously it resulted in marked edema and sloughing with scar formation. This was not evident with 5 per cent solution or less.

Subcutaneous injections of procaine base solutions of 5 per cent or less resulted in very little apparent reaction and there was prolongation of anesthesia with the higher concentrations. With both Efocaine and 10 per cent procaine base hyperemia occurred, but all evidence of it disappeared in 48 hours. Anesthesia was present for a period of 4 to 17 days with Efocaine and 8 to 16 days with 10 per cent procaine base. With 5 per cent procaine base the anesthesia ranged from 3 to 12 days.

The rationale for prolonged effect of Efocaine and procaine base is based upon the pharmacological fact that water insoluble and slowly absorbed agents produce a sustained effect. This has been demonstrated by the well known use of the hormone implants and the suspensions of the antibiotics. The anesthetic bases are insoluble in water and are slowly absorbed. Efocaine contains two of

these bases, namely 5 per cent butyl p-aminobenzoate and 1 per cent procaine base. These are soluble in the non-toxic aqueous miscible solvents, propylene glycol and polyethylene glycol-300. The latter acts as a protective polymer to stop decomposition (6,46,47,48). When this solution is diluted with aqueous fluids (serum, lymph or extracellular fluid) the anesthetic agents deposit in a crystalline form.

Procaine base suspensions uses namely aluminum hydroxide gel and methocel as suspending agents. Merthiolate 1:5,000 is added to keep the preparation sterile as procaine base is decomposed by heat. After injection of either Efocaine or procaine base suspension, a drug depot is formed which is then slowly absorbed to elaborate the anesthetic action over an extended period (49).

The results of microscopic study of tissue sections seems to indicate somewhat more reaction than that reported by Weinberg (39). The reaction with 10 per cent procaine base is too severe to warrant a clinical trial. On the basis of Weinberg's observations (39) and that of Ansbro and co-workers (6) plus the fact that the inflammatory reaction in subcutaneous tissue was mild to moderate after 14 days and nerve and muscular reaction was mild, it seems logical that Efocaine is suitable for clinical use as far as pathological reactions are concerned.

The 10 per cent procaine base causes too much tissue necrosis for clinical use, whereas, the reactions with 5 per cent procaine base are similar to those with Efocaine and warrant clinical trial.

Only one reference is made to the acute toxicity of Efocaine when injected intravenously. Ansbro and co-workers report that .6 of a ml. injected into the ear vein of one rabbit caused no immediate reaction (6). The work reported here proves it to be more toxic than equal amounts of procaine hydrochloride. With this in mind some care should be exercised in the use of this drug, making sure that large amounts of the anesthetic are not injected into the blood stream. Literature put out on this drug states that pooling of the drug should be avoided. This would tend to lessen the dangers incurred with the use of Efocaine in which intravenous injection might be made.

This danger of acute toxicity does not apply to procaine base suspensions as they have very little effect when injected intravenously.

In view of the above findings Efocaine, and 5 per cent procaine base suspensions were evaluated clinically as a means of controlling post-operative pain. This work was done in the Department of Surgery University of Nebraska College of Medicine.

Clinical Trial of Efocaine and Procaine Base Preparation.

Some reports have appeared in the literature since this work was started, on the effectiveness of Efocaine in post-operative surgery.

Ansbro and co-workers (6) and Iason et al (50) report on 64

cases in surgery of head, neck amd extremities. Post-operatively 35 patients required no narcotics, another 24 required only 1 or 2 doses. No patient required more than 4 narcotic injections.

A number of reports (6,50,51,52) on post-operative intercostal nerve block with Efocaine have been made. This allowed patients to breath more deeply and cough freely without pain and obviated the need for respiratory depressing narcotics. It appears to be an effective means of helping to prevent post-operative pulmonary complications (52).

In lower abdominal surgery (6,50) convalescence was more pleasant and earlier ambulation was facilitated with Efocaine. In 285 patients, 87 required no post-operative narcotics and 141 needed only 1 or 2 doses (49).

Efocaine has also been reported favorably for use in ano-rectal and vaginal surgery (6,50,53,54,55). Relief of post-operative pain in almost all cases is reported. Post-operative narcotic requirements were very much decreased (52,53).

Injection of Efocaine after an episiotomy resulted in a high degree of pain relief and a more pleasant convalescence was achieved (49). No local tissue reactions, systemic toxicities, nor interferences with wound healing was observed in any of the patients.

Work has been done in the Surgery Department of the University of Nebraska College of Medicine, with cooperation of the Department of Anesthesiology, on the clinical comparison of the effectiveness of Efocaine, procaine base suspensions and a combination of 2 per cent

procaine hydrochloride plus 2 per cent procaine base, in relief of post-operative pain.

A number of things have to be taken into consideration in dealing with pain, which have not been considered in previous reports. Temperament of the patient is important, some patients are stoic individuals who stand pain without too much complaint. Others are nervous individuals and readily complain of even very little pain.

With this in mind, the following things were taken into consideration in following the patients post-operatively: objective wound pain as observed by a Resident or Intern; subjective wound pain as complained of by the patient; ease of ambulation; ease of deep breathing and coughing; the number of narcotic injections per day; the first day of voluntary urination; the first day of walking and complications.

Injections were made by numbered solutions so that the observer was unaware of the type of solution used.

The following types of surgical patients were used: thoracic, abdominal and hemorrhoidectomies. The patients were followed for 7 days and the above things were observed.

A total of approximately 200 patients were tested. Major surgery such as cholecystomies, gastric resections, transthoracic repair of diaphrahmatic hernias, inguinal herniorrhaphies and appendectomies were among those done.

In general the anesthetics tested were effective in cutting down on post-operative pain and in reducing complications. No

tissue reactions were seen. There were some patients in whom the nerve blocks were not effective. Iostonic saline injections were used as controls.

It was common for patients, such as those having gastric resections or exploration of the common duct, to require either no hypodermic or else only one or two in the entire post-operative period. Post-operative atelectasis and pneumonia were largely avoided since free respiration plus coughing were possible. Ambulation occurred earlier.

Rated according to duration and effectiveness Efocaine was found to be best with 5 per cent procaine base suspension next and 2 per cent procaine hydrochloride plus 2 per cent procaine base as last.

Summary and Conclusions

Efocaine was found to have a lower $M.L.D._{50}$ (i.e. it is more toxic) than procaine base suspensions when injected into mice. It was also found to be more toxic when injected intravenously in dogs and rabbits than either procaine hydrochloride or procaine base suspensions and care should be used in its use clinically.

Procaine base suspensions were much less toxic than either procaine hydrochloride or Efocaine, when tested in mice or intervenously in animals.

Ten per cent procaine base caused too much tissue reaction to

be regarded as useful in local anesthesia. Duration of Efocaine when injected subcutaneously was slightly longer than any of the procaine base preparations. This finding was born out in clinical use also. The average duration of anesthetic activity of Efocaine as evidenced by the skin-prick technique was 14 days.

The duration of anesthesia with 5 per cent procaine base, when injected subcutaneously was 3 days.

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